the hand-corrected informal drawing of Figure 11 attached thereto as Exhibit A). Dr. Oishi states that the correct MeGA promoter sequence was obtained from a cloned MeGA promoter-containing DNA fragment that was also used in constructing the MeGA:IDUA expression construct contained in plasmid pCT22. Applicants respectfully submit that as plasmid pCT22 containing the MeGA promoter has been deposited with American Type Culture Collection (ATCC) in compliance with the provisions of the Budapest Treaty (see the accompanying Statement Regarding Deposited Seeds and Plasmids) and the correct sequence is inherent to the deposited MeGA promoter, the correction of the MeGA promoter sequence shown in Figure 11 adds no new matter.

The specification has been amended to incorporate sequence identifiers for several disclosed sequences that previously were not referenced by their identifiers or listed in the Sequence Listing. The specification also has been amended to incorporate the deposit date and the accession number for the plasmid pCT54 deposited with ATCC, International Depositary Authority. Support for the incorporated deposit date and the accession number is found in the ATCC deposit receipt and viability statement for the pCT54 plasmid, a copy of which is Exhibit 1 attached to the Statement Regarding Deposited Seeds and Plasmids submitted concurrently herewith.

The Sequence Listing has been amended to incorporate disclosed sequences that previously were unlisted (i.e., SEQ ID NOS:13-15). Support for the newly listed sequences can be found in the originally filed application at, *inter alia*, Figure 1, and page 23, line 28. The Sequence Listing also has been amended to correct errors in the sequence of the MEGA promoter shown in Figure 11 (i.e., SEQ ID NO:11). Support for this correction is as per the discussion above regarding correction of Figure 11.

Claims 19, 35 and 50 have been canceled without prejudice. The subject matter of Claim 19 has been incorporated into Claim 18, and the subject matter of Claim 50 has been incorporated into Claim 49.

Claims 1, 5, 8-10, 14, 16-18, 20, 21, 24, 25, 29, 32-34, 36-49 have been amended, and new Claims 51-70 have been added to more particularly point out and distinctly claim that which Applicants regard as the invention. Specifically, independent Claims 1, 10, 25 and 39 have been amended to distinctly claim: a method for producing, in transgenic plants and plant cells, a lysosomal enzyme which is enzymatically active; a recombinant gene construct that can be used in the method of the invention; a transgenic plant or transgenic plant cell capable of producing a lysosomal enzyme which is

enzymatically active; and a lysosomal enzyme which is enzymatically active and produced by the method of the invention. New dependent Claims 51, 55, 58 and 61 more particularly point out that the lysosomal enzyme of the claimed invention encompasses a modified lysosomal enzyme which is enzymatically active and comprises: (a) an enzymatically-active fragment of a human or animal lysosomal enzyme; (b) the human or animal lysosomal enzyme or the enzymatically-active fragment thereof having one or more amino acid residues added to its amino or carboxyl terminus; or (c) the human or animal lysosomal enzyme or the enzymatically-active fragment thereof having one or more naturally-occurring amino acid, additions, deletions or substitutions. Support for the recitations of amended Claims 1, 10, 25 and 39, and new Claims 51, 55, 58 and 61 are found in the specification at, *inter alia*, page 17, second paragraph; and page 22, third paragraph. New Claims 52, 56, 59, 62 and 67-70 more particularly point out that the lysosomal enzyme of the claimed invention encompasses α-N-acetylgalactosaminidase, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfatase, α-mannosidase and sialidase as well as certain modifications of those enzymes. Support for the recitations of these claims are found in the specification at, *inter alia*, page 19, second paragraph to page 20, first paragraph. Claims 5, 14, 29 and 42 have been amended to recite a modified lysosomal enzyme that comprises a signal peptide at the amino or carboxyl terminal. Support for this amended recitation can be found in the specification at, *inter alia*, page 22, line 24 to page 23, line 31. New dependent Claims 71-74 more particularly point out that the modified lysosomal enzyme of the claimed invention comprises a cleavable linker, which may be separated from the lysosomal enzyme by treating with a substance that cleaves the linker. Support for the recitations of these claims are found in the specification at, *inter alia*, page 24, second paragraph. New dependent Claims 75-76 more particularly point out that the claimed method encompasses recovering lysosomal enzyme comprising a detectable marker peptide by reacting with an antibody that binds the detectable marker. Support for the recitations of these claims are found in the specification at, *inter alia*, page 24, first paragraph and pages 44-46.

The amendments add no matter. Their entry and consideration are respectfully requested.

Upon entry of this Amendment, Claims 1-18, 20-34, 36-49 and 51-76 are pending and under consideration.

Applicants acknowledge the Examiner's withdrawal of the restriction requirement and determination that the claimed invention is free of prior art.

1. The First Rejection Under 35 U.S.C. § 1.112, First Paragraph Has Been Obviated

The Examiner has rejected Claims 22-24 and 36-38 under 35 U.S.C. 112, first paragraph, as the specification allegedly does not provide an enabling description of the claimed invention. Specifically, the Examiner states that the invention employs novel nucleic acid molecules (i.e., plasmids CTprol:hGC:FLAG, pCT22, and pCT54) and novel plant lines (X-11, X-27,and CT40-9) that do not appear obtainable by a repeatable method or readily available to the public. The Examiner acknowledges the seed and plasmid deposits made by Applicants but questions the public availability of the deposits. The Examiner states that if the deposits were made under the Budapest Treaty, then a statement by an attorney of record stating that the deposits were made under the Budapest Treaty and that the deposits will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein for claims 22-24, directed to the disclosed plasmids. The Examiner further states that any such statement with respect to the deposited seeds (claims 36-38) must also establish for the record that each deposit contains at least 2,500 seeds. The Examiner further notes that the specification does not comply with, *inter alia*, 37 C.F.R. § 1.809(d) with respect to disclosing the accession number and the deposit date of plasmid pCT54.

This rejection has been obviated.

Attorneys for Applicants invite the Examiner's attention to the accompanying Statement Regarding Deposited Seeds and Plasmids and Verified Statement. In the Statement Regarding Deposited Seeds and Plasmids, the undersigned attorney of record, affirms that: 1) seeds of X-11, X-27,and CT40-9 plant lines and DNA of plasmids CTprol:HGC:FLAG, pCT22 and pCT54 were deposited on September 14, 1995, September 14, 1995, August 30, 1996, September 14, 1995, August 30, 1996 and October 17, 1996, respectively, with the American Type Culture Collection (ATCC), International Depository Authority in compliance with the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure; 2) all of the deposited seeds and plasmids were viable at the time of deposit; 3) all restriction on public access to a sample of any of the deposited seeds and plasmids

will be irrevocably removed upon the grant of a patent of which the seed or plasmid is the subject; 4) access to the deposited seeds and plasmids will be afforded to the Commissioner during the pendency of the application; 5) each seed or plasmid deposit will be maintained for a period of at least five years after the most recent request for a sample of the seed or plasmid deposit was received by the ATCC and, in any case for a period of at least 30 years after the date of deposit; 6) any of the deposited seeds and plasmids will be replaced by Applicants should it become non-viable; and 7) each seed deposit contained over 2,500 seeds.

The Verified Statement establishes the identity of the pCT54 plasmid that was deposited with the ATCC. In the Verified Statement, David N. Radin, President of Croptech Development Corporation the assignee of the present application, states that the pCT54 plasmid deposited with ATCC on October 16, 1996 and assigned the accession number 97770 is the same pCT54 plasmid described in the present application.

In light of the accompanying Statement Regarding the Deposited Seeds and Plasmids and Verified Statement, Applicants submit that the enablement requirements of 35 U.S.C. 112 are satisfied with respect to the making and using of the claimed invention that require the use of any of X-11, X-27,and CT40-9 plant lines and CTprol:HGC:FLAG, pCT22 and pCT54 plasmids.

Further, as the specification has been amended to disclose the deposit date and the accession number of pCT54 plasmid, Applicants submit that the application complies with all rules and regulations governing the disclosure of accession numbers and deposit dates of deposited biological materials.

Accordingly, Applicants respectfully submit that this rejection has been obviated and request its withdrawal.

2. The Second Rejection Under 35 U.S.C. § 1.112, First Paragraph Has Been Obviated

The Examiner has rejected Claims 1-21, 25-35, and 39-50 under 35 U.S.C. 112, first paragraph, as the specification allegedly does not enable modified lysosomal enzyme comprising any type of modification, such as internal additions/deletions, non-conservative substitutions, or other chemical modifications. The Examiner contends that the art indicates that modifying amino acid sequence by internal additions/deletions of non-conservative substitutions is more likely than not to result in non-functional proteins,

and is unpredictable. The Examiner contends that certain internal positions in a protein's sequence are critical to the protein's structure and/or function. These regions are said to tolerate only relatively conservative substitutions or no substitutions. The Examiner thus concludes that undue experimentation would have been be required to make and/or use the claimed invention in its full scope. The Examiner admits, however, the application does enable modified lysosomal enzyme which is enzymatically active and which is (1) modified only by the addition of amino acid residues at the N- or C-terminus, or (2) a fragment of a naturally-occurring lysosomal enzyme, or (3) has conservative substitutions

This rejection has been obviated.

Applicants respectfully disagree with the Examiner's conclusion regarding the type of modified lysosomal enzymes that may be practiced with the disclosed invention without undue experimentation. However, in order to expedite allowance of claims, Applicants have amended the claims to recite modified lysosomal enzyme which is enzymatically active and which comprises: (a) an enzymatically-active fragment of a human or animal lysosomal enzyme; (b) the human or animal lysosomal enzyme or the enzymatically-active fragment thereof having one or more amino acid residues added to the amino or carboxyl terminus; or (c) the human or animal lysosomal enzyme or the enzymatically-active fragment thereof having one or more naturally-occurring amino acid additions, deletions or substitutions.

Applicants respectfully submit that, as admitted by the Examiner, the specification enables the claimed invention directed to such modified lysosomal enzymes. Accordingly, Applicants request the withdrawal of this rejection.

3. The Rejection Under 35 U.S.C. § 1.112, Second Paragraph Has Been Obviated

The Examiner has rejected Claim 24 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner states that Claim 24 is rendered vague and indefinite due to the recitation of a blank ATCC accession number.

This rejection has been obviated by the amendment made hereinabove to Claim 24. Applicants respectfully request the withdrawal of this rejection.

4. The Objection To The Claims Has Been Obviated

The Examiner objects to Claims 8, 20, 21, 39, 45, and 46 because of the following informalities: In claims 8 and 45, the phrase "any of claims A, B and C" should read "any of claims A, B or C." In claims 20 and 21, the recitation of a plant cell, tissue or organ which "has" a recombinant expression construct is confusing. The Examiner suggests amending the claim to recite that the plant cell, tissue, or construct is transformed with, transfected with, or expresses the recombinant construct. In claim 39, it appears that "transgenic plant cell or a cell, tissue or organ" in the second line of part (b) should read "transgenic plant or a cell, tissue or organ." In claim 46, it appears that "glucocerebrosidase **or** modified glucocerebrosidase, α-L-iduronidase or modified α-L-iduronidase" should read "glucocerebrosidase, modified glucocerebrosidase, α-L-iduronidase or modified α-L-iduronidase."

This objection has been obviated. The pending claims as amended do not have any of these alleged defects. Accordingly, Applicants respectfully request the withdrawal of this objection.

5. The Application Complies With The Sequence Rules

The Examiner objects to the application as it does not fully comply with the sequence rules. Specifically, the application is said not refer to each disclosed sequence by an assigned identifier at p. 13, line 33; p. 23, lines 28 and 29; and Figures 1, 11, 19, and 20. The Examiner also points out a possible clerical error in the sequence appearing in Figure 11.

This objection has been obviated. The specification, Figure 11, and the Sequence Listing all have been cured of the aforementioned defects. Accordingly, Applicants respectfully request the withdrawal of this objection.

CONCLUSION

Applicants believe that each ground for rejection and objection has been successfully overcome and that the claims are in condition for allowance. Allowance of the application is earnestly requested. If any outstanding issues remain, the Examiner is invited to telephone Laura A. Coruzzi at (212) 790-6431 to discuss the same.

Respectfully submitted,

Date: August 17, 1998

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Enclosures